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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/225,502	01/06/1999	PAUL A. MOORE	PF392	2400

22195 7590 11/03/2003

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EXAMINER	
VANDERVEGT, FRANCOIS P	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 11/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/225,502	MOORE ET AL.	
	Examiner	Art Unit	
	F. Pierre VanderVegt	1644	

-- The MAILING DATE of this communication app ars on the cover sheet with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 August 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-56 and 58-103* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-56 and 58-103* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) ~~Paper No(s).~~ Filed 8/4/03 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The Examiner in charge of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to F. Pierre VanderVegt, Ph.D. in Art Unit 1644.

This application claims the benefit of the filing date of provisional application 60/070,875.

Claims 1-20 and 57 have been canceled.

Claims 21-56 and 58-103 are currently pending and are the subject of examination in the present Office Action.

1. In view of Applicant's amendment and remarks filed August 4, 2003 only the following grounds of rejection are maintained.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

2. Claims 21-56 and 58-103 stand rejected under 35 U.S.C. 101 because the claimed invention lacks a credible, substantial, specific, or well-established utility.

It was previously stated (in the Office Action mailed May 5, 2003): "Applicant's arguments filed 2-11-03 have been fully considered but they are not persuasive. Applicant traverses the rejection on the grounds that the present asserted utility of binding FK506 is not implausible to one of skill in the art based on the sequence homology with FKBP65 which binds FK506, and the presence of conserved PPIase domains present in all other FKBPs and the presence of seven conserved amino acid residues shared among all other FKBP's that have been identified, these residues thought to be involved in FK506 binding interactions.

This is not found persuasive because Applicant has not shown that the recited proteins actually bind FK506, but only speculate the presence of this property in the polypeptides set forth as SEQ ID NO:s 6 and 8 based on sequence homology. Applicant contends that the FKBP65 protein disclosed in the Coss et al manuscript was believed to be a member of the FKBP family based on sequence homology and the presence of PPIase domains. However the examiner notes that the last sentence of the Abstract of said article states that the results "suggest" that FKBP65 is a new FKBP family member, not "shows" or "demonstrates".

However, even if said polypeptides bind FK506, and are in fact a member of the FKBP family, the function or utility will not have been established. The Coss et al article attached to the Applicant's amendment filed 4-29-02, comments on the functional diversity of FKBP family members, and that

though at the time of its publication FKBP65 was identified as a member of the FKBP based on sequence homology (the presence of three PPIase domains), the possible functions of FKBP65 were still unknown (see entire article, especially the last two paragraphs of the article).

Applicant contends that said functional diversity taught by Coss is related to the differences in FKBP's subcellular location and association with various intracellular complexes, and is mechanistic information which is not required for satisfying utility under 101. Applicant further contends that said differences in location or intracellular interactions does not change the fact that FKBP binding to FK506 leads to immunosuppression by inhibiting T cell proliferation and or differentiation, or that FKBP PPIase activity is inhibited by such binding. Applicant further states that the instantly recited SEQ ID NO:s 6 and 8 contain four PPIase domains and that PPIase domains contain two regions within said domains that appear to be important for binding FK506. Applicants further contend that based on this homology, it is more likely than not that said sequences are in fact novel members of the FKBP family and that they do bind FK506, and that because FK506 binding proteins (FKBP) are established and useful proteins, assignment of the instant SEQ ID NO:6 and 8 imputes the same well established utility.

However the examiner notes that said Coss article states in column 2 of the first page of the article that the inhibition of PPIase activity in itself does not appear to be responsible for the immunosuppressant effect of the drug. The examiner also notes that the specification discloses that the instantly claimed proteins binds FK506 based on sequence homology, and does not disclose that said binding of said instantly claimed proteins to FK506 leads to immunosuppression by inhibiting T cell proliferation and or differentiation. In view of the potential divers intracellular interactions, one could envisage multiple functions for said proteins. However, the examiner notes that being a family member based on sequence homology alone does not show function, as evidenced by the wide range of functions exhibited by the immunoglobulin family of proteins absent evidence to the contrary."

Applicant's arguments filed August 4, 2003 have been fully considered but they are not persuasive.

Applicant contends that the claimed invention has a "credible, substantial, specific, or well established utility" based not only on sequence homology to FKBP65, but also on several asserted "facts," the first two of which were maintained from previous responses, namely:

1. The encoded proteins of the claimed nucleic acids possess conserved PPIase domains.

2. The encoded proteins of the claimed nucleic acids possess conserved residues that are asserted to be involved in FK506 binding interactions.

Applicant presently provides the disclosure of a post-filing date reference by Shadidy et al. (Biochimica et Biophysica Acta [1999] 1446:295-307; C7 on form PTO-1449 filed August 4, 2003) as support for the utility of the instantly disclosed and claimed invention. Shadidy discloses a new member of the FKBP family named FKBP60. Applicant discloses in the response that instant SEQ ID NO: 6 is 98.8% identical to the FKBP60 of Shadidy and that the predicted PPIase domains of instant SEQ ID NO: 6 are "nearly 100% identical" to those contained in FKBP60 disclosed by Shadidy. The Examiner respectfully disagrees with Applicant's interpretation of the reference in regard to supporting utility of the instantly claimed invention.

Applicant asserts that "like all FKBPs, FKBP60 has PPIase activity that is inhibited by FK506" and that the four FK506-binding domains of FKBP60 are homologous to the 87 amino acid domain defined as the FK506-binding domain in FKBP12. This is not, however, what Shadidy, in fact, states. Shadidy discloses in the passage including Applicant's cited reference that PPIase predictive software revealed 3 PPIase domains in FKBP60 and that a "fourth area with high homology to known PPIase domains is located at position 89-118." Shadidy goes on to disclose that via the algorithms, a conserved domain of 87 aa that includes the PPIase domain has been defined as the FKBP60 domain that binds FK506. The reference further discloses, in an analysis of the comparative literature, that within the conserved domain of another FKBP, FKBP12, the conserved region contains several amino acids that form direct hydrogen bonds with FK506. However, Shadidy discloses that several, but not all residues that are involved in FK506 binding are conserved in the FK506 binding domains of FKBP60 (page 299, 2nd column, lines 29-32 in particular) and that "**[t]hese variations must lead to altered binding affinity between FKBP60 and FK506/rapamycin or may abolish binding all together**" (page 299, 2nd column, lines 36-38 in particular; emphasis added for clarity). Specifically, Shadidy points to a position which is thought to make Van der Waals contact with the pipecolinic moiety of FK506 (page 299, 2nd column, lines 38-44 in particular). Shadidy discloses that the residue is normally a Trp in most FKBPs, a Leu or Phe in some others, but is substituted with a Met residue in ALL PPIase domains of FKBP60. shadidy goes on to disclose that, although FKBP60 does have PPIase activity, this activity is inhibited "only in the presence of a very high concentration of FK506." The reference further discloses that the lack of conservation of some amino acid residues in the PPIase domains appear "to lead to a sharply reduced affinity of FKBP60 to FK506" (page 303, section 3.4 in particular). Accordingly, contrary to Applicant's assertion, FKBP60, as disclosed by Shadidy, is not "like all FKBPs."

Applicant further asserts on page 15 of the response, based upon the FKBP60 of Shadidy, that "*one skilled in the art would find it more likely than not that the protein of the instant invention. As a member of the FKBP family of proteins, would be useful in the treatment of diseases caused by an over-active immune system. For example, antibodies to this protein could be useful in treating disorders such as graft vs. host disease, rheumatoid arthritis, and inflammation.*" However, this position is not supported by Applicant's reliance upon the disclosure of Shadidy. Shadidy discloses, in a review of the literature, that FKBP65 has a C-terminal HDEL endoplasmic reticulum retention motif and has been shown to be involved in the proper folding of tropoelastin before secretion (page 296, 1st column, lines 13-26 in particular). Shadidy reports that FKBP60 similarly has an HDEL endoplasmic reticulum targeting sequence and is most likely retained there (page 301, 1st column, lines 9-27 of the text in

particular) and may act as a chaperonin (page 303, 1st column, lines 1-7 in particular). Analysis of the sequence of instantly disclosed SEQ ID NO: 6 reveals that it too possesses a known endoplasmic reticulum targeting sequence (HEEL) at its C-terminus. Therefore, relying upon the 98.8% identity between instantly disclosed SEQ ID NO: 6 and FKBP60 of Shadidy and the presence of an ER retention sequence, one skilled in the art would find it more likely than not that the protein of the instant invention is an intracellular protein and would not be physiologically available to antibodies. Contrary to Applicant's assertions on pages 16-17 of the response based upon FKBP65 activity as disclosed by Coss (J. Biol. Chem. [1995] 49(8):29336-29341; of record) the instantly disclosed protein would not be expected to exhibit the well known function of "all other FKBPs" of binding FK506 and eliciting immunosuppressive effects upon said binding. Rather, the protein of SEQ ID NO: 6 would be expected to exhibit the demonstrated function of its nearest known relative in the family, the 98.8% identical FKBP60, of "sharply reduced affinity" to FK506, casting into doubt its ability to elicit immunosuppressive effects upon said binding at reasonable therapeutic concentrations of FK506.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 21-56 and 58-103 also stand rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Conclusion

4. No claim is allowed.

4. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH

shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to F. Pierre VanderVegt whose telephone number is (703) 305-4441. The examiner can normally be reached on M-Th 6:30-4:00; Alternate Fridays 6:30-3:00. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

F. Pierre VanderVegt, Ph.D.
Patent Examiner
October 29, 2003

PHILLIP GAMBEL, PH.D
PRIMARY EXAMINER
TECH CENTER 1600
10/29/03